PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	COVID-19 case-fatality rate and demographic and socioeconomic influencers: a worldwide spatial regression analysis based on country-level data
AUTHORS	Cao, Yang; Hiyoshi, Ayako; Montgomery, Scott

VERSION 1 – REVIEW

REVIEWER	Amélie GABET Santé Publique France, France
REVIEW RETURNED	07-Sep-2020

GENERAL COMMENTS	This is an important work, well written, with a good methodology. Interesting conclusions are brought. If there is several limitations, these one are well discussed. I have very few questions for the revision: - The CFR was not adjusted/standardized for age nor sex. Consequently, the term « crude CFR » should be specified, particularly in the first results section (text, table 1 and figure 1 headings). - Although the proportion of people aged above 65 years old was not used in the final model, associations found might differed by age group. It might be usefull to add an analysis stratified by age group in the supplemental material. - Page 22 line 52: It is said « proportion of age over 60 years in populations », but in the first results' section (including text, Table 1 and figure 1) the proportion studied was those aged over 65 years old. Please homogenize. - Another limitation of the study might be the time between diagnostic and death, as no diagnostic date was available in Our World in Data I presume. This could lead to various patients' follow-up from a country to another and different CFR.

REVIEWER	Maria Pia Fantini Alma Mater Studiorum - University of Bologna
REVIEW RETURNED	07-Sep-2020

GENERAL COMMENTS	The study by Cao and colleagues aimed at assessing the relationship of key country-level sociodemographic and health indicators with COVID-19 case fatality rates. The formal analysis is conducted well, although results are not always appropriately presented and the original data have major drawbacks. The authors acknowledged most of these limitations, and discussed some key points that have the potential to be translated into concrete actions to limit the spread and fatality of COVID-19. Here are my comments: 1) Case-fatality rate (CFR) subsection, 1st paragraph: the factors

that you list as potential drivers of CFRs are all correct, but one important driver is missing here. Because COVID-19-related deaths are not clearly defined, differences in the definition of what is a COVID-19-related death might explain huge between-country variations in the reported values. This is already acknowledged in the Strengths and Limitations subsection, but I would reassert it here too.

2) Statistical analysis subsection, 5th paragraph: Please say something more about the multiple imputation of missing values. There are many ways to do it.

3) Statistical analysis subsection, 7th paragraph: Why did you use a Poisson regression analysis for the CDRs? Maybe because the mortality rate is low (rare event assumption)? Speaking of which, what link function did you use to regress the CFRs?

4) Table 1: Log transforming skewed covariates was a good choice, but presenting transformed variables makes this table unusable. Please summarize your data in the original scale.

5) Figure 1: Variable names are very tiny. Is there a way to enlarge the font or change the layout of the matrix?

6) Associations of demographic and socioeconomic variables with COVID-19 CFR subsection, line 8: a minus sign is missing before 2.23.

7) Associations of demographic and socioeconomic variables with COVID-19 CFR subsection, lines 8-11: The use of "although" is not logical, because small coefficients reinforce the lack of statistical significance. In general, I would erase this sentence because it gives the impression that the stringency index is the weakest among all predictors, while this is not true, because you are not presenting standardized beta coefficients (or at least it seems so).

8) Table 2: Please report here (o in the text) the number of low, lower-middle, upper-middle and high income countries. This might partly explain the lack of significance for some groups in the subgroup analysis.

9) Associations of demographic and socioeconomic variables with COVID-19 CFR subsection, bottom of page 15: You are listing factors that failed to achieve statistical significance, such as testing policies in lower-middle income countries. I know that P-values should not be read uncritically by just looking at the significance level; however, when multiple tests are performed (subgroup analyses, sensitivity analyses, etc.) it is likely that you have increased numbers of Type I errors. For this reason, I would remove these factors and would not discuss them as being significant in the following sections of the paper.

10) Strengths and limitations subsection, 1st paragraph: I would not cite large sample sizes as a strength of your study. You worked on aggregate data and a set of 209 records.

11) Strengths and limitations subsection, 2nd paragraph: This study has "many" limitations, not just "some" limitations.

12) Strengths and limitations subsection, 2nd paragraph: The

	limitations stated by the authors are all correct, but I would add another one. Country-level analysis may conceal huge discrepancies between subnational entities in terms of both outcomes and predictors. The case of Northern and Southern Italy is the epitome of this. Geospatial studies conducted at the subnational level could provide less biased and more "actionable" results. 13) General comment: There are quite a number of typos (e.g., "Yeman", "interpreted [in] at least"), grammatical mistakes (e.g., "may results", "Tables 1", "number of death") and colloquial expressions (e.g., "till", "the find"). 14) Last general comment: The abbreviations "CFR" and "CRF" are used interchangeably throughout the text.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name
Amélie GABET

Institution and Country
Santé Publique France, France

Please state any competing interests or state 'None declared':
none declared

Please leave your comments for the authors below
This is an important work, well written, with a good methodology. Interesting conclusions are brought. If there is several limitations, these one are well discussed.
Reply: We thank the reviewer very much for recognizing our work.

I have very few questions for the revision:
- The CFR was not adjusted/standardized for age nor sex. Consequently, the term « crude CFR » should be specified, particularly in the first results section (text, table 1 and figure 1 headings).
Reply: We have added a statement below in the first results section to clarify that the CFR and CDR are crude values:
The CFR, CDR, CVD death rate, and diabetes prevalence shown in Table 1, Figure 1, and/or following tables and figures were not adjusted/standardized for age and sex, therefore they are crude rates.

- Although the proportion of people aged above 65 years old was not used in the final model, associations found might differed by age group. It might be usefull to add an analysis stratified by age group in the supplemental material.
Reply: We thank the reviewer for the constructive comment. A supplemental Table S1 for stratified analysis by proportion of people aged above 65 years old (≤5%, 5-10%, 10-15%, and >15%) has been added. And a statement below has also been added in the results section "Associations of demographic and socioeconomic variables with COVID-19 CFR":
Because associations might differ by the proportion of the population aged 65 years or older (65+), we produced stratified estimates by the proportion of people aged 65+ (supplemental Table S1). Briefly, population size and testing policy were found to be associated with CFR in the countries with a proportion of people aged 65+ between 5% and 10%; and GDP per capita, population size, population

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density, and the proportion of smokers were associated with CFR in the countries with a proportion of people aged 65+ larger than 15%.

- Page 22 line 52: It is said « proportion of age over 60 years in populations », but in the first results' section (including text, Table 1 and figure 1) the proportion studied was those aged over 65 years old. Please homogenize.
Reply: We thank for the reviewer pointing out the error. The number should be 65 and we have corrected it in the text.

- Another limitation of the study might be the time between diagnostic and death, as no diagnostic date was available in Our World in Data I presume. This could lead to various patients' follow-up from a country to another and different CFR.
Reply: We thanks the reviewer for pointing out the limitation and we have added it in the "Strengths and Limitations" as following:
Fourthly, because no diagnostic date was available in the Our World in Data, the time between diagnosis and death was not known, which could lead to variation in patient follow-up time among the countries and, therefore, potential differences in CFR (because the CFR is calculated using person-time).

Reviewer: 2
Reviewer Name
Maria Pia Fantini

Institution and Country
Alma Mater Studiorum - University of Bologna

Please state any competing interests or state 'None declared':
None declared

Please leave your comments for the authors below
The study by Cao and colleagues aimed at assessing the relationship of key country-level sociodemographic and health indicators with COVID-19 case fatality rates. The formal analysis is conducted well, although results are not always appropriately presented and the original data have major drawbacks. The authors acknowledged most of these limitations, and discussed some key points that have the potential to be translated into concrete actions to limit the spread and fatality of COVID-19.
Reply: We thank the reviewer very much for recognizing our work.

Here are my comments:
1) Case-fatality rate (CFR) subsection, 1st paragraph: the factors that you list as potential drivers of CFRs are all correct, but one important driver is missing here. Because COVID-19-related deaths are not clearly defined, differences in the definition of what is a COVID-19-related death might explain huge between-country variations in the reported values. This is already acknowledged in the Strengths and Limitations subsection, but I would reassert it here too.
Reply: We thank the reviewer for the comment and we have highlighted the limitation in the "Strengths and Limitations" subsection as following:
• No detailed information on time from diagnosis to death and comorbidity of the COVID-19 cases is available in current study, which might bias the association in an unknown direction.
and in discussion:
In addition, there is no single globally accepted definition of COVID-19-related death, therefore the variation in the reported values of CFR could not be fully explained, and the bias derived from the difference in the definition of COVID-19-related death between the countries could not be excluded

using the data available so far.

2) Statistical analysis subsection, 5th paragraph: Please say something more about the multiple imputation of missing values. There are many ways to do it.
Reply: A more detailed description of the multiple imputation method has been added as following: The multiple imputation method was used to handle the missing values in the data. The missing values were assumed to be missing at random. A total of ten copies of the data were created, each of which had the missing values imputed by using switching regression, an iterative multivariable regression technique. Then, each complete dataset was analyzed independently. Estimates of parameters of interest were then averaged across the ten copies to give a single estimate using Rubin's rule.

3) Statistical analysis subsection, 7th paragraph: Why did you use a Poisson regression analysis for the CDRs? Maybe because the mortality rate is low (rare event assumption)? Speaking of which, what link function did you use to regress the CFRs?
Reply: Yes, because the CDR, 13.98/1,000,000 person-months globally, it is very low in the population, therefore a Poisson regression model was used for CDR. We have specified this in the manuscript.
While for CFR, it was assumed to be normally distributed among the countries and the identity link function was used.

4) Table 1: Log transforming skewed covariates was a good choice, but presenting transformed variables makes this table unusable. Please summarize your data in the original scale.
Reply: We thank reviewer for the comment. The summary of data in the original scale has been added in the table.

5) Figure 1: Variable names are very tiny. Is there a way to enlarge the font or change the layout of the matrix?
Reply: A larger Figure 1 with high resolution has been provided for publication. However, in the word file, the figure is shrunk in proportion to the page size.

6) Associations of demographic and socioeconomic variables with COVID-19 CFR subsection, line 8: a minus sign is missing before 2.23.
Reply: The missing "-" has been added.

7) Associations of demographic and socioeconomic variables with COVID-19 CFR subsection, lines 8-11: The use of "although" is not logical, because small coefficients reinforce the lack of statistical significance. In general, I would erase this sentence because it gives the impression that the stringency index is the weakest among all predictors, while this is not true, because you are not presenting standardized beta coefficients (or at least it seems so).
Reply: We agree that the meaning of the sentence is ambiguous, and we have removed it per the reviewer's suggestion.

8) Table 2: Please report here (o in the text) the number of low, lower-middle, upper-middle and high income countries. This might partly explain the lack of significance for some groups in the subgroup analysis.
Reply: The numbers of the low, lower-middle, upper-middle and high income countries have been provided.

9) Associations of demographic and socioeconomic variables with COVID-19 CFR subsection, bottom of page 15: You are listing factors that failed to achieve statistical significance, such as testing policies in lower-middle income countries. I know that P-values should not be read uncritically by just looking

at the significance level; however, when multiple tests are performed (subgroup analyses, sensitivity analyses, etc.) it is likely that you have increased numbers of Type I errors. For this reason, I would remove these factors and would not discuss them as being significant in the following sections of the paper.

Reply: The factors that are not statistically significant have been removed in the sentence, and the following sections have been revised accordingly as well.

10) Strengths and limitations subsection, 1st paragraph: I would not cite large sample sizes as a strength of your study. You worked on aggregate data and a set of 209 records.

Reply: We have revised the strength as follows:

• Our study addressed the question from a geospatial perspective.

and in discussion:

To our knowledge, this is the first study that investigated relationship between COVID-19 CFR and demographic and socioeconomic factors globally. Although numerous studies have investigated the aforementioned factors related to the COVID-19 CFR, either they investigated the question locally, or they did not approach this issue from a geospatial perspective.

11) Strengths and limitations subsection, 2nd paragraph: This study has "many" limitations, not just "some" limitations.

Reply: We have changed "some" to "many".

12) Strengths and limitations subsection, 2nd paragraph: The limitations stated by the authors are all correct, but I would add another one. Country-level analysis may conceal huge discrepancies between subnational entities in terms of both outcomes and predictors. The case of Northern and Southern Italy is the epitome of this. Geospatial studies conducted at the subnational level could provide less biased and more "actionable" results.

Reply: We thank the reviewer for pointing out this limitation, and have added the limitation as follows:

•Country-level analysis may conceal huge discrepancies between subnational entities in terms of both outcomes and predictors.

and in discussion:

Fifthly, country-level analysis may conceal huge discrepancies between subnational entities in terms of both outcomes and predictors. The case of Northern and Southern Italy is an epitome of this. In-depth geospatial studies conducted at subnational levels are expected to provide less biased and more actionable results.

13) General comment: There are quite a number of typos (e.g., "Yeman", "interpreted [in] at least"), grammatical mistakes (e.g., "may results", "Tables 1", "number of death") and colloquial expressions (e.g., "till", "the find").

Reply: We thank the reviewer very much for the careful proofreading. We have checked the manuscript thoroughly again and have corrected all of the identified typos and grammatical errors.

14) Last general comment: The abbreviations "CFR" and "CRF" are used interchangeably throughout the text.

Reply: We are sorry for the misspelling. All the CRFs have been changed to CFR.

VERSION 2 – REVIEW

REVIEWER	Amélie Gabet Santé Publique France, France
REVIEW RETURNED	16-Sep-2020

GENERAL COMMENTS	Authors replied clrearly to all questions and consequently modified the manuscript .

REVIEWER	Maria Pia Fantini Alma Mater Studiorum - University of Bologna
REVIEW RETURNED	16-Sep-2020

GENERAL COMMENTS	The authors have addressed all my comments. Well done.